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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,314	12/22/2000	Stefano Donadio	BIOP 0753 PA	2407

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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 01/21/04 CA

Office Action Summary	Application No.	Applicant(s)	
	09/720,314	DONADIO ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 36-70 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 36-70 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 22 December 2000 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement filed 03/14/2001 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. Applicant indicates a form PTO/SB/08A has been submitted, but said form is not present in the file.

Specification

The disclosure is objected to because of the following informalities:
The title on the first page of the specification contains a typographical error, where "THA" should be "THE". In addition, tetracycline is misspelled (at l. 21). In the specification, on page 23, "SEQ ID NO:" should be used in place of "SEQID N°". Appropriate correction is required.

Claim Objections

Claim 50 is objected to because of the following informalities: When referring to sequences the proper term is "SEQ ID NO:". In addition, claim 50 is improperly dependent from two claims (46 and 40). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claim 36-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention**.

Claim 36 recites the limitation "said large fragments of DNA" in part (b). There is insufficient antecedent basis for this limitation in the claim. The claim refers to "accommodating fragments...as large as 150 kb" which can mean any of the plurality of different sized fragments from one bp to 150 kb. Therefore, to refer to the preceding fragments as "said large fragments" confers ambiguity (there is no definition in the specification). Furthermore, it is unclear whether applicant is claiming that the "suitable vector" accommodates multiple fragments at the same time or just a single contiguous fragment. Moreover, the claim is indefinite because it is unclear if applicant is claiming that the "suitable vector" can introduce and stably maintain DNA fragments exclusive of the vector itself being maintained (e.g. through integration of DNA into the bacterial genome or as a replicating plasmid).

Furthermore claim 36 is unclear and indefinite because it recites that transformation occurs through specific integration where the binary vector and host genome have regions particular to such integration. It is unclear if this means homologous recombination or site-specific integration (e.g. attB/AttP).

Claim 36 also recites the term "suitable" when referring to a vector. It is unclear what "suitable" means. For example, is a vector suitable if it does not accommodate DNA as large as 150 kb. If the vector's suitability is based on the limitations that follow, use of "suitable" only confers ambiguity viz., the claim's meaning.

Claim 39 is unclear and indefinite because it recites the phrase "preferably derived from". First, there is no indication in the disclosure of what "preferably" means. Second, there is no indication what "derived from" means. The nature and number of steps required to obtain "derivative" in this case are unclear. In the extreme case a single nucleotide can be derived from the *int* region of ΦC31.

Claim 40 is unclear and indefinite because it appears to repeat limitations that are already present in the plasmids recited in the preamble. According to the disclosure pPAC-S1 and pPAC-S2 may already contain the characteristics claimed in 40(a)-(h). Therefore, it is unclear if applicant is claiming these as additional limitations, and the pPAC plasmids need to be further modified to confer the characteristics claimed. Furthermore, the claim recites the terms, "ability to accommodate", "low copy number", "increased stability" and "ease of propagation". These are indefinite terms that confer ambiguity viz., the claim's metes and bounds, and are not clearly defined in the disclosure. For example, "increased stability" and "low copy number" as compared to what reference point?

2. **Claim 55-69 recites the limitations "the [antibiotic] gene cluster". There is insufficient antecedent basis for this limitation in the claims.**

The claims are drawn to a particular antibiotic cluster (i.e. rapamycin, erythromycin and rifamycin). However, such clusters can be obtained from disparate species within the Actinomycetales order, making it unclear as to which gene cluster is claimed. It would be remedial for the claims to be amended to incorporate the indefinite article "a", instead of "the".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claims 36-39, 42-47, 53-57, 59-61, 63-65 and 67-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter (suitable vectors), which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.**

Applicant claims are drawn to methods and cells for transferring production of a natural product from an actinomycete donor organism this is the original producer of said natural product to a different actinomycete host, using a binary vector (*E. coli-Streptomyces* Artificial Chromosome) that carries a gene cluster governing the biosynthesis of the natural product, whereby said gene is inserted into the host organism through site specific recombination. Put another way, the invention is primarily drawn to a shuttle-vector for cloning, maintaining and transforming an actinomycete host with DNA up to 150 and 300 kb.

The claims read on genus of suitable vectors. The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or

by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

With regard to suitable vectors, applicant discloses a single species of suitable vector (or more specifically two versions of the same vector as shown in Fig. 2), while claiming a genus of any vector capable of accommodating DNA up to 150 kb and capable of site specific integration. Applicant has modified a previously known P1-derived Artificial Chromosome (PAC) vector capable of accommodating DNA fragments in the 150-300 kb range for cloning, maintenance and stable transformation.

From this single example, one of ordinary skill in the art cannot reliably envision other vectors that are capable of accommodating the size limitation claimed in addition to mediating site specific integration within any actinomycete host organism. Indeed there are but a few such vectors known in the art that can accommodate large (150 kb) DNA fragments (*See* Ioannou et al. Nature Genet., 6:84-9 (1994); (teaching the parent vector of applicant's modified PAC); *See also*, Tao and Zhang, Nuc. Acids. Res., 26(21):4901-09 (1998); (teaching a binary vector capable of accommodating DNA of sizes over 300 kb for cloning and stable maintenance between *E.coli* and plant cells).

Thus the disclosure and prior art are not descriptive of the complete structure of a representative number of species, which the claims encompass, as one of ordinary skill in the art cannot envision all suitable vectors based on the teachings in the specification.

4. Claims 36-39, 42-47, 53-54 and 67-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter (natural products), which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus of natural products. As the preceding discussion points out, the written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species.

With regard to natural products, the specification teaches application of the invention for rapamycin and erythromycin (Examples 72-85 and 88-101 respectively) and indicates that the methodologies taught can be extended to other clusters. However, if the gene cluster is unknown, the binary vector would be used merely to integrate a piece of DNA into a host organism. For example, one could implement applicant's invention to clone a large cluster of genomic DNA (unknown product) and identify that the host *Streptomyces* organism now contains said cluster. However, such a determination does not convey to one of ordinary skill in the art that the host organism will now produce a product. Unless the biosynthetic pathway of the product is known (i.e. the gene cluster for a given product has been identified), given the specification's teachings, it would not be possible to envision a structure to function correlation between the gene cluster integrated and the product produced. It is noted that the disclosure does propose methods for identifying potential unknown gene clusters (Spec. at 78, bottom ¶), but such a disclosure would potentially obviate an enablement rejection, not a written description rejection. Thus the disclosure is not descriptive of the complete structure of a representative

number of species, which the claims encompass, as one of ordinary skill in the art cannot envision all natural products based on the teachings in the specification.

In sum, it must therefore be considered that the disclosure is insufficient to convince the skilled artisan that applicant is in possession of the claimed genera.

5. **Claims 36-39, 42-47, 53-57, 59-61, 63-65 and 67-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the binary vectors pPAC-S1 or pPAC-S2, does not reasonably provide enablement for all vectors capable of accommodating DNA sized up to 150 kb, capable of maintenance in *E. coli* and capable of transforming any actinomycete host through site specific integration. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.**

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims: The scope/breadth of claims are broad, in that the claims are drawn to any vector capable of accommodating up to a 150 kb DNA fragment in *E. coli* and capable of mediating site specific integration in any Actinomycete host.

Nature of the invention: The invention is primarily based on a binary vector that is capable of stably maintaining DNA fragments up to 150 kb or 300 kb and facilitate site specific integration into Actinomycete hosts.

Unpredictability of the art: The unpredictability in the art is primarily based on factors affecting stability of integration, specificity of integration and limitations on the size of the target DNA integrant. For example, while the binary vector of the invention integrates into a single site in one actinomycete host (*S. erthraeus*), it could integrate into multiple sites in another actinomycete host (*S. lividans*), resulting in aberrant integration and unintended effects on an organisms functional genomics. (*See* Brown et al. J. Bacter. 170(5):2287-95, at 2287 (1988)). Moreover, there would be a great deal of unpredictability if instant invention were to be implemented in a host that is poorly characterized genetically and physiologically. For example while one species' protoplasts are amenable to plasmid uptake another may not be readily amenable without considerable manipulation. Indeed, the successful use of actinomycete species in production of natural products is primarily narrowly limited to a few well defined and well characterized species.

At minimum the host species must be genetically defined so as to ensure the intended site specific integration of the gene cluster.

State of the art: The state of the art is well developed to the extent that several actinomycete species are well characterized physiologically and genetically. However, the same assertion cannot hold true for all actinomycete species.

Furthermore, with regard to vectors capable of maintaining large foreign fragments of DNA in *E.coli*, there are only a handful of such vectors known. Construction of suitable vectors can be problematic due to chimerism, stability and maintenance in *E. coli* as well as the potential for aberrant or unsuccessful integration in a host.

Amount of guidance provided/Working Examples: The disclosure provides a single vector (or two forms of the same vector, differing only in the *int-tsr* orientation; *See* Fig. 2). In short, not all vectors capable of maintaining fragments of DNA of the given size, can be used to use the invention.

For example, even if a host contains the appropriate site-specific integration region (i.e. attB-mediated integration), given the disclosure, it would be unknown whether potential vectors would suffer from obstacles to implementing the invention, such as chimerism, insert instability, aberrant integration, or unintended homologous recombination between the vector DNA regions and host genome. Moreover, such obstacles could vary from one Actinomycete host to another for a particular vector, especially where host species has not been fully characterized. For example, transformation of a given Actinomycete host can result in site specific integration in multiple site, or the integrant may be unstable.

Only a few vectors are capable of stably maintaining large DNA in *E. coli* and only a limited number of Actinomycete species are amenable to site-specific integration as

contemplated in the disclosure (The disclosure provides a single example of a suitable host – *S. lividans* ZX7 (Spec. pp. 81-4, Ex. 102-6), as well as a list of potentially amenable strains).

Using the single disclosed vector, an artisan would not be able to use the invention commensurate with the scope of the claims, because of the substantial and reasonable amount of variability from one host species to another. In addition the level of variability, thus concomitant experimentation would increase, where the Actinomycete host and potential binary vector have not been characterized.

Amount of Experimentation Required: Given the scope and breadth of claims, the unpredictability and the level of guidance provided relative to the claimed subject matter, the skilled artisan would have had have to conduct trial and error experimentation in order to successfully practice the invention commensurate with the claims.

6. **Claims 40-41, 48-52, 55, 58, 62 and 66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention**.

The claims are drawn to or encompass the plasmid – pPAC-S1, as well as pPAC-S2, differing only in the *int-tsr* orientation. The nucleotide sequences for pPAC-S1 and pPAC-S2 have not been disclosed.

The application discloses pPAC-S1 (and pPAC-S2), which is encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a

reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

GERRY LEFFERS
PRIMARY EXAMINER

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL ATTACHMENT

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address. (See 37 C.F.R. § 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent. (See 37 C.F.R. § 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. (See 37 C.F.R. § 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 C.F.R. § 1.806).

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.